Remarks

Claims 1-4 are under examination, claims 5-16 having been canceled. Claims 17-28 were added in the Response filed November 17, 2003, but Examiner has withdrawn claims 17-28 in the Office Action dated February 24, 2004.

Response to withdrawal of claims 17-28 as being directed to a non-elected invention

Claims 17-28 were added in the Response filed November 17, 2003. The Examiner has withdrawn claims 17-28 as allegedly being directed to a non-elected invention. The Examiner asserts that the originally presented invention has been constructively elected because an action on the merits of the originally presented invention has been issued, and alleges that claims 17-28 are directed to an invention that is "independent" or "distinct" from the invention originally claimed.

The Examiner alleges that claims 17-28 constitute three groups:

Claims 17-23- drawn to a method of producing a full-length antibody in a host plant, comprising infecting a plant with two viral vectors.

Claims 24-27- drawn to a method of producing a full-length antibody in a host plant, comprising infecting a plant with a single viral vector.

Claim 28- drawn to a method of producing a full-length antibody in a host plant, comprising infecting a plant with three viral vectors.

The Examiner further asserts that the methods of the three groups require different steps and reagents, are not disclosed as capable of use together, and that each method requires a separate search which is burdensome. Applicants traverse the withdrawal of claims 17-28.

Claims 17-28 all relate to a process for producing a full-length antibody in a host plant using viral vectors. For the reasons discussed below, claims 17-28 have unity of invention and should be rejoined and included with claims 1-4 for examination on the merits.

The Examiner appears to have subjected claims 17-28 to U.S. restriction practice. See, for example, page 2 of the Office Action, where the Examiner states in item 2 that "Newly submitted claims 17-28 are directed to an invention that is independent or distinct from the invention originally claimed." The quoted passage represents, the U.S., rather than the PCT standard.

However, the present application represents the U.S. national stage of a PCT application as filed under 35 U.S.C. § 371. MPEP § 1893.03 states that prosecution of an international application which enters the national stage in the U.S. under 35 U.S.C. § 371(c) "proceeds in the same manner as for a domestic application with the exceptions that . . . (B) unity of invention proceeds as under 37 C.F.R. § 1.475," which is governed by PCT Rule 13. Unity of invention under PCT Rule 13 is satisfied when there is a technical relationship among those inventions defined by the claims which involves "one or more of the same or corresponding special technical features." This unifying special technical feature is that which defines a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. PCT Rule 13.2 and the PCT Administrative Instructions, Annex B, Part 1(b).

Here, the special technical feature is one or more recombinant viral vectors for systemic infection of a host plant, which vectors comprise nucleic acid sequences encoding antibody heavy and light chains and which produce a full-length antibody in the host plant. Claims 1-4, which are under examination, as well as all of claims 17-28, contain this feature.

Claim 1 is drawn to a method of producing a full-length antibody in a host plant, comprising infecting a plant with two recombinant viral vectors. Claims 17-23, 24-27, and 28 are drawn to a method of producing a full-length antibody in a host plant, comprising infecting a plant with at least two, one, or three recombinant viral vectors, respectively. Also, performing the method recited in claims 1-4 or in 17-23, 24-27, and 28 necessarily results in systemic infection of the host plant and production of a full-length antibody. Thus, claims 17-23, 24-27, and 28 not only have unity of invention with one another, but also with claims 1-4.

The Examiner alleges that the claims are "distinct" (and therefore presumably lack unity of invention) because the claimed processes require different steps and reagents. There is no prohibition under PCT Rule 13.2 against processes with different steps and reagents if the claimed processes produce the same product and all contain the special technical feature (see PCT Rule 13.2 and PCT Administrative Instructions, Annex B, Part 1(a-d)). Here, the method of claims 17-28, whether using one or multiple viral vectors, results in systemic infection and production of a full-length antibody in a host plant. Since elected claims 1-4 and claims 17-28 possess the same special technical feature, all pending claims 17-28 have unity of invention and should be examined together.

The Examiner also alleges that the methods of claims 17-28 are not capable of use together with each other or with the method of claims 1-4. PCT Rule 13 does not prohibit process claims with the same technical features from being examined in a single application, even if they are not capable of use together. Rather, PCT Rule 13 allows for such claims to be examined together in a single application if all claims contain the same or similar special technical feature. As discussed above, claims 17-28 all share the same special technical feature with elected claims 1-4. Claims 17-28 therefore have unity of invention with the claims under examination and should be examined together with claims 1-4.

Examiner also alleges that the method of each claim group requires a separate search, which is burdensome. Examiner has given no explanation at all to support a contention that searching the three allegedly different inventions within claims 17-28 poses a serious burden. Applicants assert that because claims 1-4 and 17-28 encompass the use of recombinant viral vectors to systemically infect and produce a full-length antibody in a host plant, a search of one claim group would necessarily uncover art pertaining to recombinant viral vectors encoding antibody chains expressed in a plant (were such art to be found). It is therefore unlikely that a search of one claim group would reveal no art that is pertinent to the others, and such a search should not be a serious burden on the Examiner. In any case, PCT Rule 13 does not provide that lack of unity of invention arises if a search of allegedly different inventions is burdensome.

Examiner had previously characterized elected claims 1-4 as being drawn to a method for producing an antibody in a host plant using a recombinant virus, and did not specify the number of recombinant viral vectors used (page 2 of the Restriction Requirement mailed November 7, 2001). In fact, elected claims 1-4 recite that two recombinant viral vectors are used in the claimed method. Applicants respectfully submit that claims 17-28, which also recite the production of a full-length antibody in a host plant with a recombinant viral vector, are therefore also drawn to the originally elected invention.

In any case, elected claims 1-4 and claims 17-23 are drawn to methods of producing a full-length antibody in a host plant using two recombinant viral vectors. Claims 17-23 should therefore be rejoined with elected claims 1-4 for further examination.

For the reasons described, claims 17-28 have unity of invention with elected claims 1-4. Applicants respectfully request reconsideration of the ruling withdrawing new claims 17-28 from consideration. Applicants request that claims 17-28 be examined on the merits with claims 1-4.

Response to rejection under 35 U.S.C. 103(a)

Claims 1-4 stand rejected under 35 U.S.C. § 103(a) as obvious over U.S. Pat. No. 5,316,931 to Donson et al. ('931) in view of Ma et al., 1994, Eur. J. Immunol. 24:131-138 (Ma), and Scholthof et al., 1996, Ann. Rev. Phytopathol. 34:299-323 (Scholthof).

Applicants respectfully traverse the rejection.

To support a case of *prima facie* obviousness, a combination of references must: (1) suggest to those of ordinary skill in the art that they should make the claimed invention, and (2) reveal to those of ordinary skill in the art that they would have a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in Applicant's disclosure. *In re Dow Chemical Company*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Here, the cited references, either alone or in combination, do not suggest the claimed methods nor indicate that they could be practiced with any degree of success.

Claims 1-4, and claims 17-23 and 28, recite methods of producing an antibody in a plant by infecting the plant with multiple recombinant viral vectors. Claims 24-27 recite a method of producing an antibody in an infected plant with a viral vector comprising a nucleic acid sequence encoding a movement protein of a first virus and a nucleic acid sequence encoding a capsid protein of a second virus. The claimed vectors carry viral sequences needed for viral replication and systemic infection of the host plant, and for expression of antibody heavy and light chain peptides. The expressed antibody heavy and light chain peptides are assembled in the plant into a full-length antibody.

Donson '931 discloses systemic infection of plants with a single viral vector and expression of a foreign gene sequence in the infected plant. Donson '931 does not suggest the use of multiple recombinant viral vectors to express antibody sequences in plants, as recited in claims 1-4 and in withdrawn claims 17-23 and 28. Moreover, Donson does not teach a recombinant viral vector comprising a nucleic acid sequence encoding a movement protein of a

first virus and a nucleic acid sequence encoding a capsid protein of a second virus, as recited in claims 21 and 24-28.

Contrary to the Examiner's allegations, Donson '931 does not show the actual production of antibodies using a viral vector. In fact, Donson '931 merely provides a long list of proteins and polypeptides – including antibodies – and speculates that these proteins and polypeptides, could be produced by a viral vector in a plant (column 14, lines 59-68). As admitted by the Examiner, Donson does not specify any methods to accomplish antibody production and assembly. Therefore, Donson does not teach "successful" production of antibodies in a plant, much less a method for producing a full-length antibody in a host plant using a recombinant viral vector as recited in the present claims.

One of ordinary skill in the art at the time of the invention would not have been motivated by the teachings of Donson '931 to use multiple viral vectors to infect plants and express an antibody. One skilled in the art would not believe that, by following the teachings of Donson '931, a full-length antibody could be successfully produced in a plant with the vectors as recited in the present claims. Applicants respectfully submit that the Examiner has misinterpreted the arguments presented in the previous Response. The Examiner alleges that complex defenses by plants against infection is a problem that can be overcome, because Donson '931 teaches that a viral vector can cause systemic infection in a plant. However, Donson '931 merely teaches that a "single" viral vector can cause systemic infection in a plant. One of ordinary skill in the art would not assume that multiple viral vectors could overcome the complex defenses of plants merely because Donson '931 had infected a plant with a single vector. As described in the previous Response filed November 12, 2003, a host plant can recognize viral nucleic acids as well as nucleic acids encoding foreign genes, and can mount sequence-specific responses via virus-induced gene silencing (VIGS) or post-transcriptional gene silencing (PTGS) (Waterhouse et al., 2001, Nature, 411:834-842; submitted with November 12, 2003 Response). For example, Waterhouse showed that a plant sensitized to the β-glucuronidase gene develops resistance to viral vectors containing β-glucuronidase sequences.

Thus, one skilled in the art would have recognized, at the time the present application was filed, that plant cells exposed to one viral vector may be resistant to infection or replication of another viral vector with the same or similar sequences. Multiple viral vectors, especially those

which express the same or similar nucleic acid sequences, would therefore not necessarily be expected to replicate or cause systemic infection in a host plant. Absent any specific motivation to use multiple vectors, one skilled in the art would consider methods which use a *single* viral vector to deliver foreign genes superior to methods using multiple viral vectors.

Ma does not remedy the deficiencies of Donson '931. Ma teaches that monoclonal antibodies can be expressed and assembled in transgenic plants in which the sequences encoding the foreign polypeptides have been inserted into the plant genome. Ma does not disclose the use of viral vectors to deliver and express foreign gene sequences in plants, nor does Ma discuss the desirability of delivering foreign genes into plants with viral vectors. Moreover, Ma does not disclose or suggest that multiple recombinant viral vectors can be introduced into a plant by infection with the vectors, that multiple vectors can systemically infect a plant, or that expression and assembly of the antibody sequences can occur in the infected plant. In addition, the present specification is the first demonstration of plant virus vectors producing a full-length antibody in plants (page 47, lines 27-30). Therefore, contrary to the assertion of the Examiner, it would not have been obvious to incorporate the teachings of Ma into Donson's method to produce antibody heavy and light chains by introducing separate viral vectors into one plant, resulting in an assembled, full-length antibody, as is presently claimed.

Examiner alleges that one skilled in the art would have been motivated to produce the antibody light chain and the heavy chain separately (as in Ma) because antibodies are complex proteins consisting of several heteromeric chains. Neither Donson '931 nor Ma teach or suggest that separate antibody chains can be produced from multiple viral vectors (or indeed in a single viral vector); nor do these references provide a motivation to do so. As discussed above, one of ordinary skill in the art would not have been motivated to use multiple vectors in plants, because of the known responses by plants to viral gene sequences.

Examiner also alleges that one skilled in the art would have been motivated to use viral vectors instead of a transgenic approach (as in Ma), because Scholthof discloses advantages of plant virus gene vectors for transient expression of foreign proteins in plants versus transgenic gene expression (citing the Scholthof abstract). The Examiner asserts that one skilled in the art would have had a reasonable expectation of success that separate viral vectors encoding antibody light and heavy chains would assemble into a full-length antibody in an infected plant, because

Donson '931 allegedly teaches successful production of antibodies using a viral vector in one plant and Ma allegedly teaches a successful method of assembling antibodies. As described above, Donson '931 does not teach successful production of antibodies in a plant and Ma does not teach the use of viral vectors to express antibodies.

Scholthof does not correct the deficiencies of Donson '931 and Ma. Scholthof is a review article which discusses the development and use of various plant viral vector systems, including the use of two complementary plant viral vectors and the use of plant viral vectors for antigen presentation. However, Scholthof does not contemplate the use of multiple viral vectors to express separate heavy and light chain antibody genes in plant cells, much less teach that it would be advantageous to do so.

In fact, Scholthof teaches away from the use of multiple recombinant viral vectors to infect host plants and express foreign genes. See pg. 311 of Scholthof, which states that "[c]omplementation of artificially constructed viral molecules that can carry a foreign gene" with multiple recombinant viral vectors has "mostly failed" because the multiple recombinant viral vectors undergo recombination events that regenerate the wild-type virus. Because the regenerated virus is wild-type, it necessarily lacks the foreign gene sequence of interest and is no longer useful for expressing the foreign gene.

Moreover, claims 21 and 24-28 recite use of viral vectors, either single or multiple, for expressing separate antibody heavy and light chain genes, in which the vectors comprise capsid and movement proteins from different virus types. Scholthof does not teach or suggest that such vectors can be made or used for any purpose, let alone to express antibody heavy or light chains.

Thus, Scholthof does not, either alone or in combination with Ma and/or Donson '931, suggest the presently claimed methods, because the combination of the three references does not result in a method for producing a full-length antibody, wherein a plant is infected with viral vectors which express antibody heavy and light chains, or wherein the vectors comprise capsid and movement proteins from different virus types.

Ma does not disclose the use of viral vectors to deliver foreign gene sequences into plants, nor does Ma discuss the desirability of delivering foreign genes with viral vectors. There is also no teaching or suggestion in Donson '931 or Scholthof that multiple viral vectors as recited in claim 1 are preferable to single viral vectors for delivering foreign genes to plants. As

discussed above, one skilled in the art would be skeptical that infection with multiple viral vectors would result in systemic infection of the host plant with both vectors, with concomitant expression of the foreign gene sequences throughout the plant, as recited in claims 1-4 and in withdrawn claims 17-23 and 28. Furthermore, neither Donson '931, Ma, nor Scholthof teach multiple vectors comprising sequences encoding a viral movement protein and a viral capsid protein from different viruses, as recited in claims 21 and 24-28. The cited references would therefore not motivate one skilled in the art to produce the presently claimed methods, nor would these references provide a reasonable expectation that the claimed methods could be successfully practiced. Claims 1-4, 17-23 and 28 are therefore not obvious over the cited references.

As stated above, claims 21 and 28 recite methods of producing an antibody in a plant by infecting a host plant with multiple vectors encoding a viral movement protein from one type of virus, and a viral capsid protein from another type of virus. These claims are patentable over Donson '931, Ma, or Scholthof, because none of these references disclose, either expressly or inherently, multiple vectors comprising sequences encoding a viral movement protein and a viral capsid protein from different viruses.

Claims 24-27 recite methods of producing an antibody in a plant by infecting a host plant with a single viral vector. The claimed vector comprises sequences encoding an antibody heavy and light chain, and sequences encoding a viral movement protein from one type of virus, and a viral capsid protein from another type of virus. These claims are patentable over Donson '931, Ma, or Scholthof, because none of these references disclose, either expressly or inherently, a single vector comprising sequences encoding a viral movement protein and a viral capsid protein from different viruses.

The expression of viral movement and capsid proteins from different viruses, as recited in claims 21 and 24-28, allows the claimed viral vectors to avoid the plant viral defense systems discussed above, so that the vector can successfully replicate, infect the host plant systemically, and produce the full-length antibody. Claims 21 and 24-28 are patentable over Donson '931, Ma and Scholthof, because none of these references, either alone or in combination, teach movement and capsid protein complementation which allows avoidance of viral defense systems, systemic infection, and production of full-length antibodies in plants. As stated in the present specification at page 17, line 26 to page 18, line 4:

> An **unexpected** aspect of the present invention is the discovery that the coat protein gene of a first class of virus (e.g., TMV) ciscomplements the long distance movement and encapsidation functions of a second class of virus (e.g., A1MV) (See Example 5). Thus the complementation in the present invention can be applied rather broadly across various strains and even various genera including viruses and plants. The complementation of certain functions thus achieved has the advantage in, among other things, reducing the selective pressure by the host plant thereby facilitating the movement, assembly, or replication of the recombinant viral vectors and in extending the host range of the recombinant viruses.

(emphasis added).

In fact, articles referenced by Scholthof on page 314 in the section entitled "Virus Movement" teach away from the claimed invention of claims 21 and 24-28, by teaching that interactions between capsid proteins and movement proteins are unimportant in infection and movement of viruses through a host plant (De Jong and Ahlquist, Proc. Natl. Acad. Sci. USA, 1992, 89:6808-6812, submitted herewith; Giesman-Cookmeyer et al., 1995, Virology, 213:38-45, submitted herewith). For example, De Jong et al. teach that movement protein functions are independent of specific features of viral coat proteins (see abstract and introduction). Giesman-Cookmeyer et al. teach transfection of single virus vectors into transgenic plants and that movement proteins of different viruses can be functionally homologous without being structurally homologous (see abstract).

There is nothing in any of the cited references to suggest that expression of viral movement and capsid proteins from different viruses would confer a selective advantage for movement of the vector(s) through the host plant. Thus, claims 21 and 24-28 are believed to be patentable over the references discussed above.

Conclusion

Claims 1-4 and 17-28 are believed in condition for allowance. Claims 17-28 possess unity of invention with the invention of claims 1-4, and should be rejoined with claims 1-4. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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